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Evaluation of vascular changes in intermediate uveitis and retinal vasculitis using swept-source wide-field optical coherence tomography angiography

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ABSTRACT

Purpose To evaluate vascular changes in patients with intermediate uveitis with or without retinal vasculitis using swept-source wide-field optical coherence tomography angiography (OCTA).

Methods This is a prospective cross-sectional study. Consecutive patients with intermediate uveitis were evaluated using wide-field OCTA. Wide-field OCTA and en-face OCT images were analysed for the presence of capillary non-perfusion and reduced perfusion, disruption of ellipsoid zone, and abnormalities on en-face wide-field retinal thickness maps, respectively, and compared with fluorescein angiography (FA) findings in a subcohort.

Results 164 eyes of 88 patients with intermediate uveitis were included. Areas of capillary non-perfusion and reduced perfusion were more frequently observed in the choroidal OCTA slab (33.3% and 49.4%), choriocapillaris (CC; 31.4% and 48%) and deep capillary plexus (DCP; 9.6% and 34.6%) than in the superficial capillary plexus (SCP; 5% and 26.3%), respectively. Intermediate uveitis with vasculitis presented more frequently with non-perfusion and hypoperfusion in the DCP (p=0.003 and p=0.05, respectively) and SCP (p=0.007 and p=0.005, respectively) than intermediate uveitis without vasculitis. Peripheral capillary leakage on FA correlated with the presence of perivascular, macular and generalised thickening on en-face wide-field thickness maps (p=0.007). Ischaemia on FA was significantly associated with non-perfusion on wide-field OCTA in SCP and DCP (p=0.019 and p=0.027, respectively).

Conclusion Changes in the choroid, CC and DCP are more frequently found than in the SCP on wide-field OCTA in intermediate uveitis. While wide-field OCTA is a reliable tool to detect capillary non-perfusion in intermediate uveitis, it was not helpful in determining disease activity.

Trial registration number NCT02811536.

INTRODUCTION

Intermediate uveitis (IU) is a type of uveitis mainly localised to the vitreous and the ciliary body that lacks chorioretinal inflammation.[1] Concomitant retinal vasculitis is often found in this disease, involving commonly the peripheral retinal veins.

Fluorescein angiography (FA) is sensitive in the diagnosis of retinal vasculitis and also an important diagnostic tool to detect macular oedema, optic disc oedema and other complications.[2] However, FA is invasive and has a substantially limited depth resolution; thus, the middle and deeper capillary plexus are difficult to visualise.[3] Moreover, leakage of dye can limit our ability to evaluate adjacent capillary perfusion.[4] Indocyanine green angiography (ICG) allows the assessment of uveitis with choroidal involvement. However, the exact localisation of the inflammation within the choroid using ICG may be challenging.[5]

Optical coherence tomography angiography (OCTA) is a new, non-invasive imaging method that provides volumetric data of retinal and choroidal layers.[6] OCTA has already shown its advantage in evaluating foveal microvascular changes in retinal vascular diseases as it is able to visualise vascular flow in the deep capillary plexus (DCP) as well as in the choriocapillaris (CC) and the choroid.[6] This may be of importance as previous studies could illustrate that the deeper vessels rather than the superficial vascular plexus are more affected and impaired in retinal vascular diseases such as diabetic retinopathy.[7] Furthermore vascular changes may be more easily detected using OCTA compared with other imaging modalities.[8] Moreover, OCTA can provide separate evaluation of abnormalities in the retinal and choroidal circulations.[9]

The wide-field OCTA improves the narrow field of view of traditional OCTA. Previous studies[10 11] have shown that wide-field OCTA successfully detected vascular abnormalities seen on FA in retinal diseases such as diabetic retinopathy and polypoidal choroidal vasculopathy. But inherently OCTA cannot detect vascular staining or leakage, and its role therefore is somewhat different in uveitis than in other vascular disorders dominated by structural changes such as capillary loss and others.

The aim of our study is therefore to identify and evaluate vascular changes in patients with IU with or without retinal vasculitis using wide-field OCTA and compare findings with wide-field FA in a subcohort.

METHODS

Study population

This was a prospective cross-sectional study. Consecutive patients presenting with IU with or without retinal vasculitis at the Department of Ophthalmology of Inselspital, University of Bern, between October 2016 and October 2017 were enrolled in this study.

Subjects were eligible if the following criteria were met: adult patients diagnosed with non-infectious IU with or without retinal vasculitis. The diagnosis of IU fulfilled the criteria of the Standardization in Uveitis Nomenclature (SUN)[12] and the disease activity was based on the National Eye Institute (NEI) system.[13] The diagnosis of retinal vasculitis was based on the ophthalmoscopic criteria of a history or presence of intraocular inflammation, perivascular exudates, intraretinal haemorrhage or cotton-wool spots on ophthalmoscopy and evidence of vascular occlusion or profound leakage on fluorescein angiogram (FA).[14 15] Concomitant peripheral vascular sheathing as regularly seen in IU was not deemed to be retinal vasculitis. Investigational work-up included chest X-ray, QuantiFERON-TB Gold in tube test, serological testing for syphilis and Lyme disease, and immunology tests including HLA-B51, antinuclear antibodies, ACE, lysozyme, interleukin-2 receptor and antineutrophil cytoplasmic antibodies. Furthermore, an MRI of the brain was performed to screen for cerebral vasculitis and demyelinating lesions.

Subjects with any ocular condition that would interfere with good-quality image acquisition were excluded. Patients with history of ocular trauma or other retinal diseases, such as diabetic retinopathy, hypertensive retinopathy, central serous chorioretinopathy and macular degeneration, and optic nerve diseases such as glaucoma or optic neuropathy, were also excluded.

Acquisition of OCTA image

All patients underwent ophthalmic examination including Snellen best-corrected visual acuity, slit-lamp examination, intraocular pressure and dilated fundus examination. Wide-field FA was performed with Heidelberg Spectralis HRA+OCT (Heidelberg Engineering, Heidelberg, Germany) using the 102° lens. At 5 min peripheral sweeps of all quadrants were acquired. If FA was not performed on the same day, the most recent FA images were compared with OCTA images; in this case, the FAs were only included for comparison, if there was no reported change in disease activity or therapy and performance of FA was not more than 28 days apart from OCTA acquisition. ICG imaging, which was typically performed for initial work-up, was also reviewed to rule out posterior involvement.

All patients underwent imaging with the swept-source (SS)-OCT (PLEX Elite 9000; Carl Zeiss Meditec, Dublin, California). Patients were imaged using wide-field montage OCTA scan consisting of five 12×12 mm scans, covering about 80°–90° of the posterior pole (one centred on the fovea, the others centred on the temporal-superior, temporal-inferior, nasal-superior and nasal-inferior quadrants; figure 1). The individual 12×12 mm scans were reviewed for the presence of alignment errors and artefacts due to floaters and manually corrected if present. After quality check the 12×12 images were montaged using the automatic montage export function available on the device.

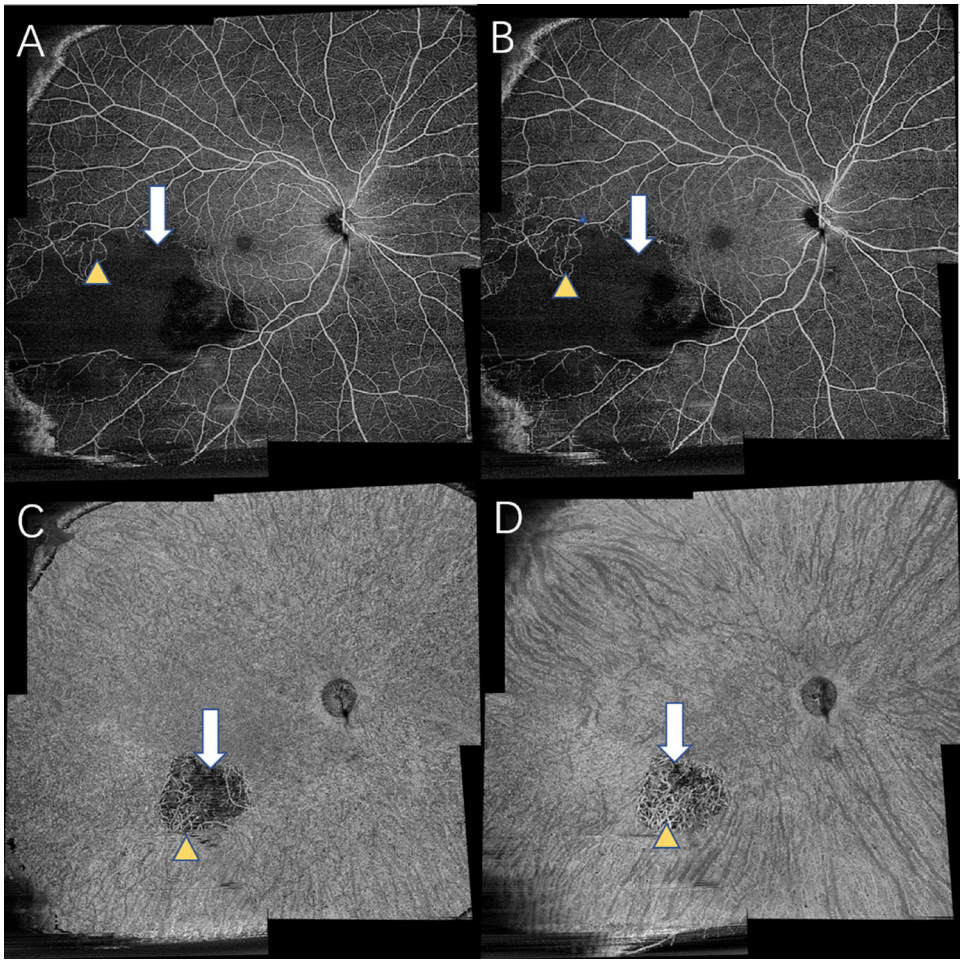

Figure 1 Non-perfusion (white arrow) and reduced perfusion (yellow triangle) in the montage scans. (A) Superficial capillary plexus, (B) deep capillary plexus, (C) choriocapillaris and (D) choroid.

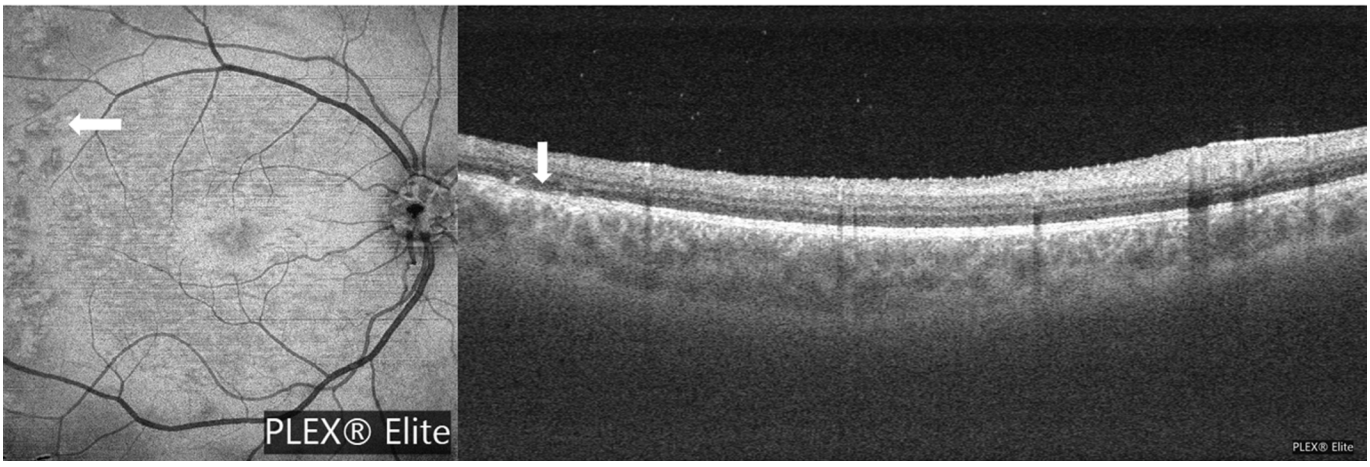

Figure 2 Disruption (=hyporeflectivity) on the ellipsoid zone of the en-face wide-field slabs. White arrows depict exemplary areas of ellipsoid zone disruption.

To analyse the individual vascular layers, the custom segmentation of the device was used. The superficial capillary plexus (SCP) extends from the internal limiting membrane (ILM) to the inner plexiform layer (IPL), and the DCP from the IPL (inner boundary) to the outer plexiform layer (outer boundary). The CC extends from 29 μm beneath the retinal pigment epithelium(RPE) to 49 μm beneath the RPE, and the choroidal layer has a thickness of 51 μm and extends from 64 μm to 115 μm below Bruch's membrane.[16]

Qualitative analyses of wide-field OCTA images, en-face wide-field slabs and thickness maps were independently conducted by two masked Bern Photographic Reading Center trained readers (MT and MRM), at different time-points and in different orders. In cases of discrepancies a consensus grading was performed. All images were evaluated on the instrument display screen in a standardised, dimmed environment. Wide-field montage OCTA images were examined for the presence of capillary non-perfusion and reduced capillary perfusion in SCP, DCP, CC and choroid. Capillary non-perfusion was defined as an area of total and profound capillary loss ≥1/4 of the disc area[9] (figure 1). Reduced capillary perfusion referred to smaller areas of reduced capillary density (figure 1). The individual structural OCT B-scans were evaluated for the presence of cystoid macualr oedema(CME), epiretinal membrane and disruption of the ellipsoid zone. The en-face wide-field slabs were individually examined for the presence of disruption of the ellipsoid zone (figure 2). The en-face wide-field retinal thickness maps (boundaries ILM and RPE; figure 3) were examined for the presence of perivascular thickening, macular thickening, peripapillary thickening, generalised thickening and retinal thinning (figure 4). The degree of retinal thickness was graded according to the colour-coded thickness maps. Cool colours (green and blue) represent decreased thickness, while warm colours (yellow, orange and red) represent increased thickness.[17] Qualitative analysis of capillary network abnormalities was then compared with FA. Peripheral capillary leakage was compared with flow changes on the wide-field OCTA. The 12×12 OCTA scans centred on the optic nerve head were carefully reviewed for non-perfusion/hypoperfusion and correlated to optic nerve head leakage visible on FA. Furthermore, the perfusion abnormalities found on the central 12×12 scans were correlated to macular leakage. The structural OCT B-scans were used to identify epiretinal membrane and . CME

Statistical analysis

Statistical analysis of the data was performed using SPSS V.23.0. Descriptive statistics (percentages, means and SD) were computed for demographic and clinical variables. Intergrader reproducibility is indicated by Cohen's kappa. Kappa values up to 0.2 indicate a slight agreement, while values between 0.21 and 0.40 are considered as fair, 0.41–0.60 as moderate, 0.61–0.80 as substantial and 0.81–1 as almost perfect agreement, respectively.[18] Phi and Cramer's V was used for qualitative data analysis. A minimal value of $p \leq 0.05$ was considered statistically significant. P value correction for multiple testing was employed using false discovery rate.

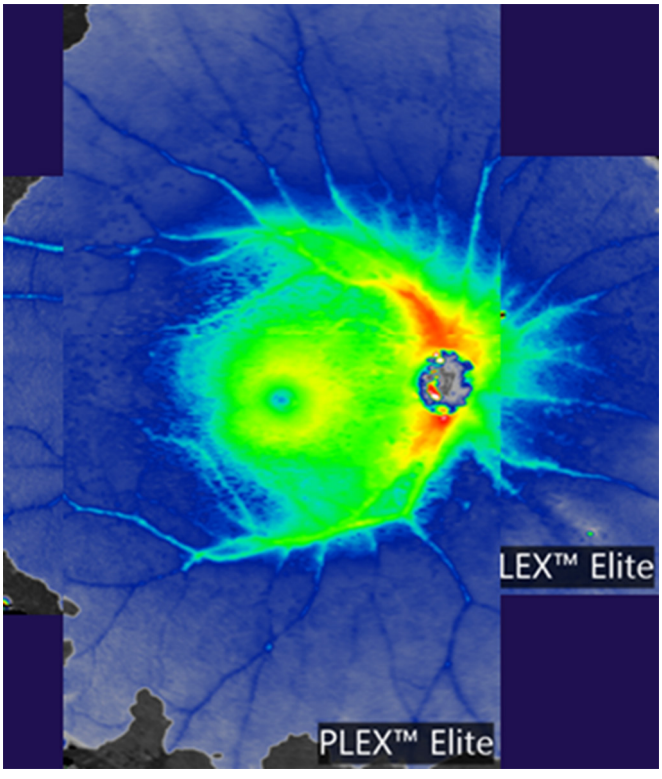

Figure 3 Example of colour-coded en-face wide-field retinal thickness map.

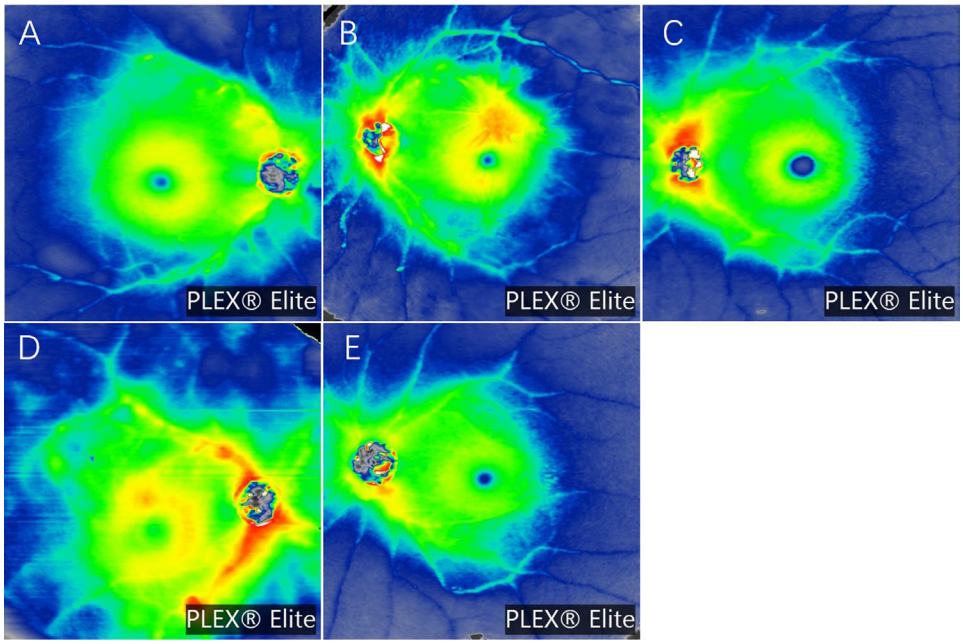

Figure 4 En-face wide-field thickness maps. (A) Normal, (B) macular thickening, (C) peripapillary thickening, (D) perivascular thickening and generalised thickening, and (

RESULTS

One hundred and sixty-four eyes from 88 patients were included in this study (mean age 45.5±18.7 years, 54 women [61.4%]). One hundred and twenty-four eyes (75.6%) had IU and 40 eyes (24.4%) had concomitant retinal vasculitis. The mean Snellen acuity was 0.9±0.5 (range: 0.01–1.2). Bilateral disease was found in 86%. Thirty-six eyes (22%) exhibited clinically active inflammation based on the SUN/NEI criteria. Forty-five patients (51.1%) were on systemic conventional synthetic or biological disease-modifying antirheumatic drugs.

Eight eyes were retrospectively excluded from the analysis because of poor OCTA image quality. Thus, 156 (95.1%) eyes, including 120 (76.9%) with IU and 36 (23.1%) with concomitant vasculitis, were evaluated. Out of these, 11 eyes have no FA images available. The intergrader agreement was substantial to almost perfect, ranging from 0.69 to 0.85 (Cohen's kappa). Online supplementary table 1 summarises the results of intergrader agreements for each individual evaluated parameter. Baseline clinical characteristics, FA and SS-OCT findings are summarised in table 1.

En-face OCT wide-field findings

The en-face wide-field thickness maps (figure 4) are summarised in table 2.

There was an association between peripheral capillary leakage on FA and the presence of perivascular, macular and generalised thickening on en-face wide-field thickness maps (p=0.007, corrected [corr] p=0.04), but there was no significant correlation between clinically assessed disease activity and the findings on wide-field thickness map. Disruption of the ellipsoid zone was visible in 36 eyes (23.1%) on the en-face wide-field slabs (figure 2), which was associated with the presence of CME (p≤0.0001, corr p=0.03) and ERM (p≤0.0001, corr p=0.03).

Characteristics of eyes with IU with/without retinal vasculitis on wide-field OCTA

Table 3 summarises the prevalence of capillary non-perfusion and reduced capillary perfusion on wide-field OCTA (figure 1) of eyes with IU with and without vasculitis in the individual customised retinal and choroidal slabs.

In general, capillary non-perfusion and reduced perfusion were more frequently observed in the choroid, CC and DCP than in the SCP (table 3). This high prevalence of CC and choroidal reduced perfusion seems noteworthy given that only five eyes (3.2%) showed an area of obvious chorioretinal atrophy, which was always unrelated to underlying IU. While IU with vasculitis presented more frequently with non-perfusion and hypoperfusion in the DCP (p=0.003, corr p=0.04 and p=0.05, corr

Table 1 Baseline clinical characteristics

Age (years)	46±19
Sex	
Male	36 (41.4%)
Female	51 (58.6%)
Laterality	
Unilateral	5 (5.7%)
Bilateral	82 (94.3%)
BCVA (decimal Snellen)	0.9±0.5
Baseline treatment	
Disease-modifying antirheumatic drugs	45 (51.1%)
Associated systemic disease/aetiology	
Sarcoidosis	20 (12.2%)
Latent tuberculosis	8 (4.9%)
Behçet	24 (14.6%)
Idiopathic	112 (71.8%)
SS-OCT findings	
Epiretinal membrane	53 (34%)
Cystoid macular oedema	28 (18%)

BCVA, best-corrected visual acuity; SS-OCT, swept-source optical coherence tomography.

Table 2 Findings on the en-face wide-field thickness maps

En-face wide-field thickness maps	Prevalence (%)
Perivascular thickening	10 (6.4)
Macular thickening	36 (23.1)
Peripapillary thickening	26 (16.7)
Generalised thickening	11 (7.1)
Retinal thinning	12 (7.7)

Table 4A The wide-field FA findings in the subcohort compared with wide-field OCTA

Wide-field FA findings	Prevalence (%)
Peripheral capillary leakage	36 (76.6)
Peripheral capillary dropout	13 (27.7)
Hot disc	15 (31.9)
Macular leakage	22 (46.8)

FA, fluorescein angiography; OCTA, optical coherence tomography angiography.

p=0.2, respectively) and SCP (p=0.007, corr p=0.04 and p=0.005, corr p=0.04, respectively) than IU without vasculitis, there was no significant difference in terms of non-perfusion and hypoperfusion in the CC (p=0.48, corr p=0.7 and p=0.79, corr p=0.87, respectively) or choroid between those two patient groups (p=0.1, corr p=0.46 and p=0.4, corr p=0.7, respectively) (table 3). There was no significant difference in capillary non-perfusion or reduced perfusion in the SCP (p=0.5, corr p=0.7 and p=0.9, corr p=0.93, respectively) or DCP wide-field slabs (p=0.6, corr p=0.74 and p=0.2, corr p=0.6, respectively) between active and inactive eyes.

Comparisons between OCTA and FA findings

There were 47 cases with comparable FAs with a mean period between OCTA and FA of 10.7±14.7 days. Details can be found in table 4A and B. Table 4A and B Comparison of wide-field FA findings and wide-field OCTA findings.

There was no association between peripheral capillary leakage on FA and non-perfusion or reduced peripheral perfusion on wide-field OCTA in the SCP (p=0.36, corr p=0.7 and p=0.88, corr p=0.93, respectively), DCP (p=0.94, corr p=0.94 and p=0.7, corr p=0.83, respectively), CC (p=0.5, corr p=0.7 and p=0.22, corr p=0.6, respectively) or choroid (p=0.47, corr p=0.7 and p=0.59, corr p=0.74, respectively). However, capillary dropout and ischaemia visible in 27.7% on FA was associated with capillary non-perfusion on wide-field OCTA in the SCP and DCP, respectively (p=0.019, corr p=0.1 and p=0.027, corr p=0.12, respectively), but missed statistical significance after p value correction. Considering FA as gold standard, the sensitivity and specificity in the detection of capillary dropout in the SCP on OCTA were 15% and 97%, respectively (false negative rate=85%, false positive rate=3%). The sensitivity and specificity in the detection of capillary dropout in the DCP were 24% and 94%, respectively. Peripheral capillary non-perfusion or hypoperfusion of the CC and choroid was not associated with capillary dropout on FA (CC: p=0.39, corr p=0.7 and p=0.4, corr p=0.7; choroid: p=0.58, corr p=0.74 and p=0.31, corr p=0.7, respectively). Peripapillary capillary non-perfusion or hypoperfusion in the SCP (p=0.49, corr p=0.7 and p=0.7, corr p=0.84), DCP (p=0.49, corr p=0.7 and p=0.13, corr p=0.46), CC (p=0.75, corr p=0.86 and p=0.49, corr p=0.7) and choroid (p=0.22, corr p=0.58 and p=0.5, corr p=0.7) was not associated with the presence of a hot disc. Also macular leakage on FA was not associated with non-perfusion or hypoperfusion on the central OCTA slabs.

DISCUSSION

We here present a prospective cross-sectional study using wide-field SS-OCTA images to evaluate vascular changes in patients with IU with or without retinal vasculitis. Our paper evaluated vascular changes using wide-field OCTA in IU and retinal vasculitis as previous uveitis studies have focused on vascular changes on the central 3×3 mm OCTA scans.[19 20] Our data show that montage wide-field OCTA seems to be a promising tool to detect microvascular alterations of the retina and choroid. Thus, flow void within 80°–90° can be directly seen and may not be indirectly evaluated using a central 3×3 or 6×6 scan. In contrast to FA, where the assessment of the capillary plexus is limited due to the trilaminar pattern of the network by leakage and by poor resolution of the DCP,[3 20] OCTA can individually visualise the peripapillary plexus, the DCP, the CC and the choroid.

Qualitatively on the wide-field OCTA, the DCP was more frequently involved than the SCP. This is in line with the findings of previous studies[12–14 19] on retinal diseases such as vein occlusion and diabetic retinopathy, in which more profound alterations have also been observed in the DCP than in the SCP. The reason for this may be that, unlike the superficial retinal capillaries, the deep capillaries are not directly connected to arterioles, and are therefore more vulnerable to ischaemia.[21] A previous paper by Spaide[22] investigated the microvascular flow abnormalities associated with retinal vasculitis in areas of active

Table 3 Capillary non-perfusion and capillary reduced perfusion in SCP, DCP, CC and choroid

	Intermediate uveitis without vasculitis		Intermediate uveitis with concomitant retinal vasculitis	
	Non-perfusion	Reduced perfusion	Non-perfusion	Reduced perfusion
Montage wide-field scans				
SCP	3 (2.5%)	25 (20.8%)	5 (13.9%)	16 (44.4%)
DCP	7 (5.8%)	37 (30.8%)	8 (22.2%)	17 (47.2%)
CC	36 (30%)	57 (47.5%)	13 (36.1%)	18 (50%)
Choroid	36 (30%)	57 (47.5%)	16 (44.4%)	20 (55.6%)
Peripapillary area				
SCP	1 (0.8%)	14 (11.7%)	0 (0%)	6 (16.7%)
DCP	2 (1.7%)	13 (10.8%)	0 (0%)	7 (19.4%)
CC	5 (4.2%)	12 (10%)	5 (13.9%)	12 (33.3%)
Choroid	7 (5.8%)	16 (13.3%)	3 (8.3%)	12 (33.3%)

CC, choriocapillaris; DCP, deep capillary plexus; SCP, superficial capillary plexus.

Table 4B The wide-field OCTA findings in the subcohort compared with wide-field FA

	Capillary non-perfusion	Capillary reduced perfusion
Wide-field OCTA findings		
SCP	2 (4.3%)	12 (25.5%)
DCP	4 (8.5%)	15 (31.9%)
CC	15 (31.9%)	23 (48.9%)
Choroid	16 (34%)	22 (46.8%)
Peripapillary area		
SCP	1 (2.1%)	8 (17%)
DCP	1 (2.1%)	9 (19.1%)
CC	4 (8.5%)	9 (19.1%)
Choroid	3 (6.4%)	9 (19.1%)

CC, choriocapillaris; DCP, deep capillary plexus; FA, fluorescein angiography; OCTA, optical coherence tomography angiography; SCP, superficial capillary plexus.

vasculitis. Similar to our results, he found qualitatively larger areas of absent flow in the DCP compared with the SCP.[22]

Although wide-field OCTA seems a promising additional tool for the assessment of peripheral retinal ischaemia, it currently has limited potential to fully replace wide-field FA. Although the prevalence of reduced capillary perfusion found on the wide-field OCTA in the SCP was similar to the prevalence of capillary non-perfusion on wide-field FA, the association of this finding between FA and OCTA did not remain statistically significant after p value correction. And although the specificity for the detection of capillary non-perfusion on OCTA was high, the sensitivity was rather low. However, our assessment was qualitative and a 12×12 scan pattern with a lower resolution of 24 µm was used. Previous studies could show that OCTA may be even more sensitive than FA in detecting perifoveal capillary abnormalities, such as hypoperfusion and non-perfusion on the ocular sarcoidosis eyes and retinal vasculitis,[23 24] and a recent report illustrated that wide-field OCTA depicts the extensive capillary non-perfusion of the peripheral retina better than FA in some retinal vasculitis cases.[25] Thus, with the progress of OCTA in terms of acquisition time and resolution, wide-field OCTA may soon become a sensitive and quantitative tool for the direct assessment of peripheral capillary dropout of the individual retinal and choroidal vascular layers.

Interestingly, although none of the OCTA data showed an association with peripheral capillary leakage on FA, there was a correlation between peripheral capillary leakage on FA and perivascular-peripapillary and macular thickening on en-face wide-field thickness maps. In keeping, a previous study on patients with Birdshot chorioretinopathy has shown that perivascular thickening on thickness maps corresponds to vasculitis and may be used to follow phlebitis and disease activity in patients with respective disease.[17] Our findings broaden the spectrum of evaluable diseases, which makes en-face thickness maps a promising, additional tool to follow patients with uveitis.

A surprisingly high percentage of patients had some CC and choroidal flow void. In some cases, alterations of the choroidal circulation were explainable by the presence of peripapillary chorioretinal atrophy or chorioretinal atrophy elsewhere; however, in the majority of eyes, decreased flow was independent of respective finding. Although several studies evaluated the choroidal involvement using OCTA in posterior uveitis,[4 26 27] nothing is so far known about the choroidal involvement in patients with IU using OCTA. In a recent paper, Wintergerst and coauthors[28] quantitatively analysed the CC perfusion in central 3×3 mm OCTA scans and also revealed that altered CC perfusion is frequently present in IU. The choroidal blood supply is still poorly understood. Anatomical postmortem studies describe the CC and choroid as highly anastomosed network, while in vivo studies indicate an end-arterial circulation.[29] Whether IU and vasculitis without visible posterior involvement may cause indirect decrease in flow signal or a blockage phenomenon due to inflammation of the CC and choroid needs definitely further evaluations. Recent studies on healthy eyes quantified CC flow void and found an age-dependent decrease of CC in healthy subjects (oral presentation IRIS, Los Angeles, 2018; and OCT and Retina forum, Milan, 2018).[30] It may be therefore possible that inflammation in the eye exaggerates the normal age-dependent decrease of CC and choroidal flow.

The inclusion of both eyes to increase the number of observations must be considered as potential limitation, as it may have biased our results. Overall, based on all the findings, we can conclude that OCTA is a valuable imaging modality to assess peripheral capillary non-perfusion in patients with IU with or without vasculitis and enables the evaluation of the perfusion status of the SCP, DCP, CC and choroid of about 80°−90°.

Contributors MT: analysis of data, evaluation of data, writing the manuscript. TC: collecting data, critical review of the paper. MSZ: collecting data, evaluation of data, critical review of the paper. WH: statistical analysis, critical review of the paper. SW: financial support, collecting data, critical review of the paper. MRM: study design, analysis and evaluation of data, statistical analysis, critical review of the paper.

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Competing interests None declared.

Patient consent for publication Obtained.

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